REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 12-27, 31, 32, and 34-39 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 12-27, 31, 32, and 34-39 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirements. This rejection is obviated by the amendments to the claims.

Claims 15-17 have been rejected under 35 U.S.C. §101. This rejection is obviated by the amendment to claims 15-17.

Claims 12, 13, 18, 22, 35, 36 and 38 have been rejected under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Santamaria et al. The examiner states that Santamaria discloses cytomegalovirus primed peripheral blood mononuclear cells from seropositive subjects which are stimulated by anti-CD-3 coated onto polystyrene beads plus interleukin-2 falling within the scope of applicants' claims. This rejection is respectfully traversed.

Santamaria discloses a method for culturing T lymphocytes from subjects seropositive for cytomegalovirus by stimulating with IL-2 and anti-CD3 antibodies only in the very beginning (in the absence of feeder cells and specific CMV antigens). The purpose of Santamaria's study is to develop a new method for the expansion of lymphocytes capable of long term growth (culture). Accordingly, Santamaria does not disclose or teach the use of expanded lymphocytes for treatment of CMV or any other viral infections, and therefore the T lymphocytes from long term culture would not be administered back to the same seropositive subject from which they were derived. Claims 12 and 13 are also amended to exclude cytomegalovirus infected patients. This is supported by the disclosure, at page 8, line 1 of the present specification, of cytomegalovirus infection as being one of many viral infections. Therefore, Santmaria cannot anticipate or make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 12, 14-18, 23-27, 35 and 37 have been rejected under 35 U.S.C. §102(b) as being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being obvious over Koenig et al. The examiner states that Koenig's disclosure of compositions comprising autologous lymphocytes

from an AIDS patient activated with IL-2 and OKT3, which activated autologous lymphocytes at doses of $28x10^9$, $12x10^9$ and $13x10^9$ were resuspended in normal saline and human serum albumin, and reinfused into the patient for treatment of the patient's HIV infection falls within the scope of applicant's claims. The examiner asserts that at the very least the claimed invention is rendered obvious because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. The examiner further states that although Koenig appears to disclose the use of soluble OKT3 instead of solid phase OKT3, the claim is directed to a product not a process (this position is incorrect because rejected claims 14, 23-27, and 37 are indeed method/process claims), and as such, the examiner holds that the burden is on applicant to show that the activated lymphocytes using solid OKT3 are different from activated lymphocytes using soluble OKT3. This rejection is respectfully traversed.

The OKT3 monoclonal antibody used by Koenig is indeed soluble, as conceded by the examiner, and therefore does not meet the limitation of "anti-CD3 antibodies in a solid phase" as recited in the present claims. Accordingly, Koenig simply cannot anticipate the presently claimed invention.

In addition, there is a difference between using solid phase antibodies and soluble antibodies in activating lymphocytes. Attached hereto is a copy of Sekine et al., *Biomed. Pharmcother.* 47:73-78 (1993), which clearly demonstrates on page 77, column 2, lines 4-12, that immobilized (solid phase) anti-CD3 antibody effectively amplified and propagated CD4 lymphocytes to great volume compared with soluble anti-CD3 antibody. Moreover, Tokoro et al., *Eur. J. Immounol.* 26:1012-1017 (1996), a copy of which is also attached hereto, reported that immature T cells undergo apoptosis when stimulated by anti-CD3 antibodies that are not in the solid phase.

The propagation efficiency of activated T cells using the solid phase anti-CD3 antibodies according to the presently claimed invention would be much higher than using soluble anti-CD3 antibodies. This difference between the presently claimed invention and the applied Koenig reference is significant and is certainly not obvious.

Furthermore, Koenig teaches in the abstract that "Unexpectedly, infusion was followed by a decline in circulating $CD4^+$ T cells and a rise in viral load." This means that the HIV virus, for which $CD4^+$ T cells are the host, was propagated by infusion of an HIV-1 seropositive individual with an expanded autologous cytotoxic T lymphocyte clone

directed against HIV-1 nef protein. Koenig further teaches at page 331, second and third paragraphs, that "the transient increase of $CD4^+$ cells, especially after the first CTL infusion, was followed by marked declines in $CD4^+$ counts... a marked (fourfold) rise in proviral DNA was observed within eight months of the first infusion, and further increases were found after the second infustion." In the first sentence in the Discussion section on page 332, Koenig reports that clinical progression and CD4 decline occurred despite the presence of CTLs to nef and other HIV proteins.

Given the teachings of Koenig, one of ordinary skill in the art would not look to Koenig for a method for treating a viral infection according to the present claims because Koenig's method instead showed an increase in viral load and disease progression. Koenig actually provides a disincentive and a teaching away from the presently claimed method for treating viral infections.

Reconsideration and withdrawal of the rejection(s) are therefore respectfully requested.

Claims 12-27, 31, 32, and 34-39 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Ochoa et al. (U.S. Patent 5,443,983) in view of Rosenberg (U.S. Patent 4,690,915), Melder et al., the acknowledged prior art, Wallace et al., Rooney et al., Babbit et al. (U.S. Patent 5,766,920),

Ochoa et al. (U.S. Patent 5,296,353), Santamaria et al. and Buseyne et al. This rejection is respectfully traversed.

In the primary Ochoa '983 reference and in six of the eight secondary references (Rosenberg, Melder, Wallace, Rooney, Babbit, and Ochoa '353) cited and applied by the examiner, T cells are only stimulated with IL-2 and/or anti-CD3 antibodies for use in anti-viral therapy. However, the use of autologous lymphocytes in antiviral therapy is very different from the use of autologous lymphocytes which are derived from a virally infected patient in anti-viral therapy. It is quite clear that none of these references disclose, teach or suggest the use of lymphocytes collected from the blood of a virally infected patient. This feature of "autologous lymphocytes derived from a virally infected patient" is positively recited in the present claims. Thus, one of ordinary skill in the art would not be motivated from the combination of disclosures and teachings of Ochoa '983, Rosenberg, Melder, Wallace, Rooney, Babbit and Ochoa '353 to use as lymphocytes that are to be activated those autologous lymphocytes derived/collected from a virally infected patient.

The examiner has applied Santamaria in combination with the other applied references for its disclosure of stimulating/activating lymphocytes collected from blood of virally infected patients. However, it is clear to one of

ordinary skill in the art that Santamaria is merely using polystyrene monosized particles coated with agonistic antibodies to induce the long term growth (cultivation) of antigen-specific T cell lines for autoimmune studies. Because Santamaria is directed to developing a long term cultivation method, there is nothing in Santamaria's disclosure that would suggest or motivate one of ordinary skill in the art to use autologous T lymphocytes derived from virally infected patients in combination with the disclosures of the other remaining applied references to treat viral infections, even if they all share a common feature of activation of lymphocytes with IL-2 and anti-CD3 antibodies.

Furthermore, as taught by Koenig, a prior art reference cited and applied separately by the examiner, the infusion into a patient of expanded autologous CTLs was unexpectedly followed by a decline in circulating $CD4^+$ cells and rise in viral load with subsequent disease progression. This is most certainly a teaching that would motivate one of ordinary against combining the separate isolated disclosure of Santamaria with the disclosures and teachings of Ochoa '983, Rosenberg, Melder, Wallace, Rooney, Babbit and Ochoa '353 to arrive at the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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